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MODULATION OF OXIDATIVE STRESS AND CARDIAC BIOMARKERS IN ISO-INDUCED MYOCARDIAL INFARCTION IN RATS: ROLE OF BONE MARROW-DERIVED MESENCHYMAL STEM CELL THERAPY

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ABSTRACT

Background: Isoproterenol-induced MI is associated with oxidative stress and disruption of membrane integrity. BM-MSCs have shown promising cardio-protective and reparative effects through immunomodulatory and antioxidant mechanisms. The current study aims to evaluate the role of BM-MSC in modulating oxidative stress and cardiac biomarkers in ISO-induced MI in rats.
Methods: BM-MSCs were isolated from the femur and tibia of rats and cultured. 30 SD male rats were divided into 3 groups. G1 (control), G2 (MI group), and G3 (BM-MSC treated group). A fresh ISO solution was prepared. MI was induced by S.C. administration of 85 mg/kg/day of ISO for 2 consecutive days. After the last dose of ISO, BM-MSC were administered I/V to G3. On the 28th day, rats were euthanized, and blood and heart tissue samples were obtained. Oxidative stress, antioxidants, and cardiac biomarkers were measured, and RT-PCR was performed to estimate cardiac gene expression. Histopathology of heart tissue was performed.
Results: ISO administration resulted in significantly increased levels of oxidative stress and cardiac-specific biomarkers, as well as increased expression of cardiac-specific genes. BM-MSC treatment was associated with significant declines in oxidative stress and cardiac biomarker levels, as well as decreased expression of cardiac genes. Significantly elevated antioxidant levels were observed with BM-MSC treatment. Histology showed improved myocardial architecture in G3.
Conclusion: BM-MSC therapy modulates oxidative stress and cardiac biomarkers, enhances antioxidant defense, and thus serves as a promising therapeutic strategy for ISO-induced MI.

KEYWORDS: Myocardial infarction, Isoproterenol-induced MI, Bone marrow stem cells, Cardiac repair, Oxidative stress

1. INTRODUCTION

Isoproterenol (ISO) is a synthetic β-adrenergic agonist and is commonly used to induce myocardial infarction (MI) in experimental models. The use of ISO is a safe, non-invasive, and efficient technique compared with surgical occlusion of the coronary artery to induce MI (Asiwe et al., 2024). The prevailing theory regarding the mechanism of ISO-induced MI is that, due to catecholamine overstimulation, there is oxidative stress, increased antioxidant utilization, inflammation, calcium overload, and energy depletion. The researcher suggested that the ISO-induced MI model disrupts cellular redox processes, which leads to the generation of reactive oxygen species (ROS) and free radicals. These ROS and free radicals ultimately caused lipid peroxidation. Malondialdehyde (MDA), which is a lipid peroxidation product, is produced in greater amounts and is an indicator of oxidative stress. The disruption of myocardial membrane integrity and permeability caused by free radicals is further exacerbated by calcium influx through apoptotic and necrotic pathways (Anwar Zarkasi et al., 2020; Hareeri et al., 2023). The interaction of free radicals and ROS with cellular lipids, nucleic acids, and proteins leads to cellular damage. The body has a powerful, intrinsic protective antioxidant enzyme system, including glutathione (GSH) and superoxide dismutase (SOD). This antioxidant enzyme system is inhibited by oxidative stress and thereby further potentiates myocardial injury. Disruption of the myocardial membrane causes release of cardiac-specific enzymes such as CK-MB, lactate dehydrogenase (LDH), cardiac troponin I (cTnI) and cardiac troponin T (cTnT), and atrial natriuretic peptide (ANP) (Rihan & Sharma, 2024).

Myocardial infarction is a chronic crippling disease that ultimately leads to cardiac failure. Emerging evidence suggests the role of stem cell-based therapy in treating MI (Yamada et al., 2022). Bone marrow-derived mesenchymal stem cells (BM-MSCs) have gained popularity in the treatment of MI. BM-MSCs can be successfully differentiated into cardiomyocytes and have cardiac regenerative and reparative potential, especially after MI (Farag et al., 2024). BM-MSCs have paracrine, immunomodulatory, and anti-inflammatory properties. Due to these properties, BM-MSCs have

the potential to reverse inflammation and oxidative stress, thereby modulating the infarcted myocardium towards a normal, healthy heart (Chang & Li, 2023).
The current study aims to investigate the role of BM-MSC in modulating oxidative stress and cardiac biomarkers in ISO-induced MI in rats.

2. METHODS

2.1. Ethical Approval

The study was approved by the University of Lahore Review and Ethics Board (Ref-IMBB/BBBC/24/906-A). Before, during, and after the experiment, internationally accepted ethical guidelines for animal care, handling, and minimizing animal suffering were strictly followed. Moreover, the ARRIVE guidelines for in vivo experiments reporting were also followed (Klabukov et al., 2023). Both in vitro and in vivo experiments were included in our study. A schematic overview of the study design and key findings is presented in the Graphical Abstract.

2.2. Animals used in the study

The 30 Sprague-Dawley (SD) male rats weighing 120-180g were purchased from the Institute of Molecular Biology and Biotechnology of the University of Lahore animal house. The animals were kept under standard conditions with standard laboratory food and water. Light and temperature were kept constant, and rats were acclimated for two weeks before the start of the study.

2.3. Isoproterenol (ISO)

ISO was obtained as a crystalline powder from Sigma-Aldrich, USA. A fresh solution of ISO was formed immediately prior to the administration of the dose. The dose of ISO was calculated to be 85mg/kg body weight for the rats. 2 ml of ISO was subcutaneously (SC) administered to the rats for two consecutive days, with an interval of 24 hours.

2.4. In vitro experiment

Isolation and culturing of BM-MSC

BM-MSCs were isolated by flushing the resected tibia and femur of 5 SD male rats obtained from the University of Lahore animal house. The collected bone marrow was cultured in Dulbecco's modified Eagle medium (DMEM) with the following composition: fetal bovine serum 10%, penicillin (100 U/ml), and streptomycin (100 mg/ml). The cells were incubated at 37°C in a CO_2 incubator. After 80% confluency and after the 4th passage, cells were used for further experimentation. Images of cells were taken from the Floid cell imaging station for analysis of the morphology of cultured cells.

2.5. In Vivo experiments

2.5.1. Experimental design

The 30 SD male rats were distributed into 3 groups (n=10 per group). Group 1, comprised of normal, healthy controls received 0.1ml/100g, SC of normal saline for two consecutive days with a 24-hour interval. Group 2, the MI group, MI induced with ISO, the dose calculation and route of administration were mentioned above. Group 3, the BM-MSC treatment group. Each rat in this group was administered 0.5 ml of BM-MSCs suspended in culture media, in a single dose. BM-MSC were administered after the final ISO dose. The rats were observed for 28 days, during which their weight, behavior, or any other warning signs were observed. The rats were euthanized on the 28th day. American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals and institutional guidelines were strictly followed for euthanasia. A 200mg/kg dose of ketamine hydrochloride was intraperitoneally injected, and during the injection, the animal was placed in a head-down position. After the injection, the animal was placed in a cage. Respiratory and cardiac activity were measured to confirm the death. Ten milliliters of intracardiac blood samples were collected. Samples were divided into two: one for serum separation and the other for whole blood.

2.5.2. Blood parameters

Total leukocyte count (TLC) and C-reactive protein (CRP) levels were measured using an automated analyzer according to the manufacturer's guidelines.

2.5.3. Analysis of cardiac-specific biomarkers

CK-MB, lactate dehydrogenase (LDH), cardiac troponin I (cTnI), cardiac troponin T (cTnT), and atrial natriuretic peptide (ANP) levels were measured as per protocols provided with the commercially available kits (Abcam Rat ELISA kits).

2.5.4. Antioxidants and Oxidative Stress Markers

MDA, GSH, and SOD levels were measured using commercially available kits (Cayman Chemical).

2.5.5. Gene expression analysis

When the rats were sacrificed, the heart was taken out and washed twice with normal saline immediately. One piece was cut and placed in TRIzol for RT-PCR analysis of cardiac markers, including cTnT, cTnI, and ANP. After cDNA synthesis, RT-PCR was done.

2.5.6. Histopathological analysis

The heart tissue was fixed in 10% formalin and embedded in paraffin. Then, sections were cut and deparaffinized, and the deparaffinized sections were stained with hematoxylin and eosin (H&E) for further histopathological analysis.

2.6. Statistical Analysis
Data was entered, analysed, and interpreted using Graphpad Prism 8.4.2. One-way ANOVA and two-way ANOVA were used for comparisons within and between groups. A p-value less than or equal to 0.05 will be considered statistically significant.

3. RESULTS
3.1. In Vitro Morphology Analysis of BM-MSC
As shown in Figure 1 (a, b), the BM-MSCs images from the floid cells imaging station. As demonstrated in the figure, round, floated cells were on day 0 of the culture (Figure 1a). Cells with characteristic features of BM-MSC, with spindle-shaped, adherent, interconnected cells, were observed on day 7 of the culture (Figure 1b).

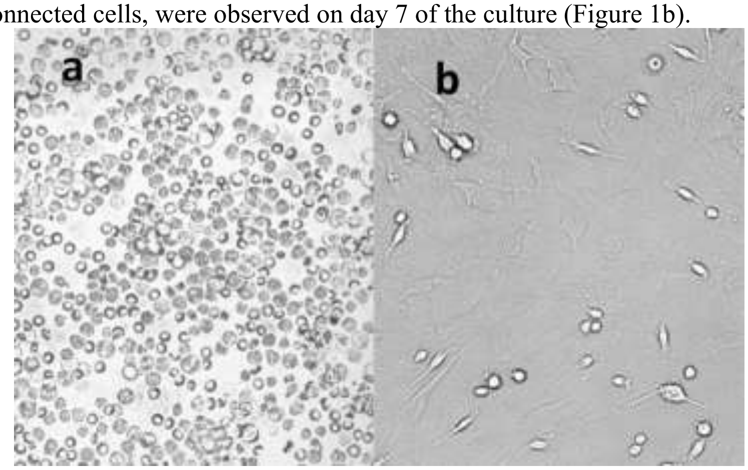

Figure 1. Morphology analysis of BM-MSC in vitro. (a) Image taken at day 0 of culture. (b) Image on day 7, with the characteristic spindle-shaped morphology of cultured BM-MSC.

3.2. In vivo experiment results
3.2.1. Effect of BM-MSC treatment on TLC and CRP
Figure 2 showed the effect of BM-MSC treatment on TLC and CRP levels in ISO induced MI. As demonstrated in the figure, levels declined in the BM-MSC when compared to the injury group. There is a statistically significant difference in the injury group versus the BM-MSC and control group. These results show improvement in inflammation in MI when treated with BM-MSC.

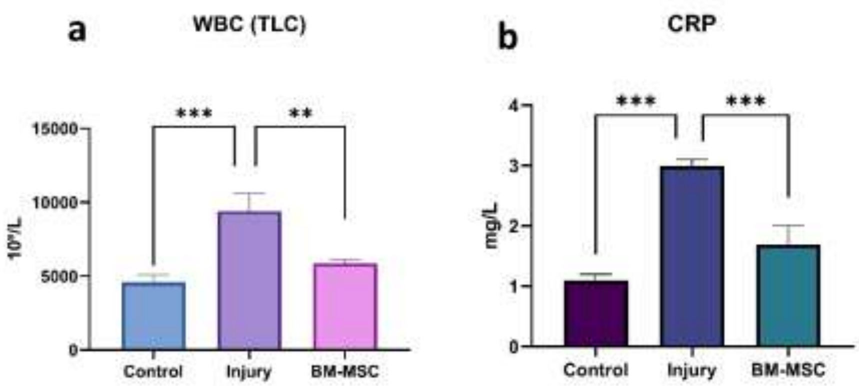

Figure 2. Effect of BM-MSC treatment on TLC and CRP levels in vivo.
Results expressed in mean ± SD, **p= .004, *** p <.001

3.2.2. Effect of BM-MSC treatment on cardiac-specific biomarkers
ISO administration leads to increased levels of cardiac-specific biomarkers. As demonstrated in Figure 3 (a-e), levels of CK-MB, LDH, cTnI, cTnT, and ANP were significantly raised in the injury group when compared to the BM-MSC group. The levels were significantly reduced after treatment with BM-MSC. These results were suggestive of improved cardiac repair after BM-MSC treatment.

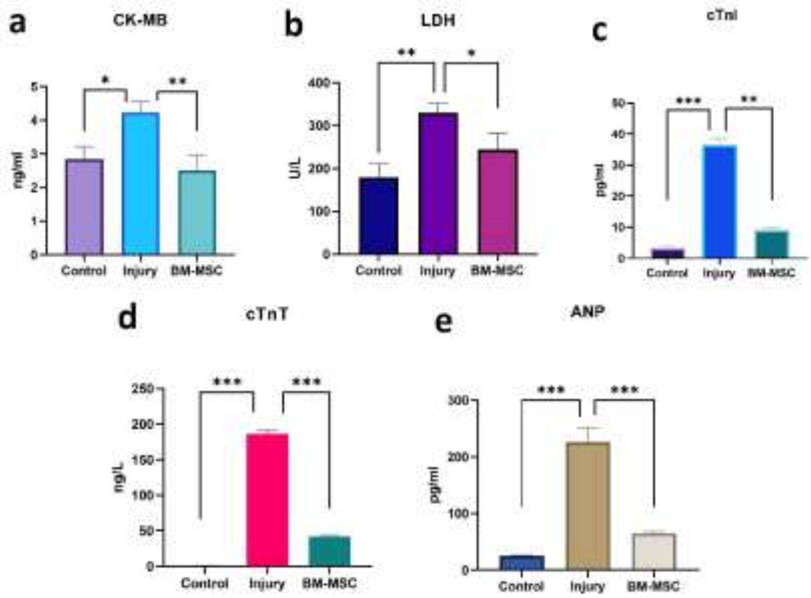

Figure 3. Effect of BM-MSC treatment on cardiac-specific biomarkers. (a) CK-MB levels (b), LDH levels (c), cTnI levels (d), cTnT levels (e), and ANP levels in all groups in vivo.

Results expressed in mean ± SD, *p=.048, **p=.003, *** p <.001

3.3. Effect of BM-MSC treatment on antioxidant and Oxidative stress markers

Figure 4 demonstrated the effect of BM-MSC on ISO-induced-MI in rats. As shown in the figure, levels of GSH and SOD were increased in the BM-MSC group as compared to the injury group. Levels of MDA were significantly reduced in the MI group as compared to the BM-MSC group. These results suggested that treatment with BM-MSC improved oxidative stress induced by ISO, as well as improved antioxidant levels, thus enhancing heart repair after MI.

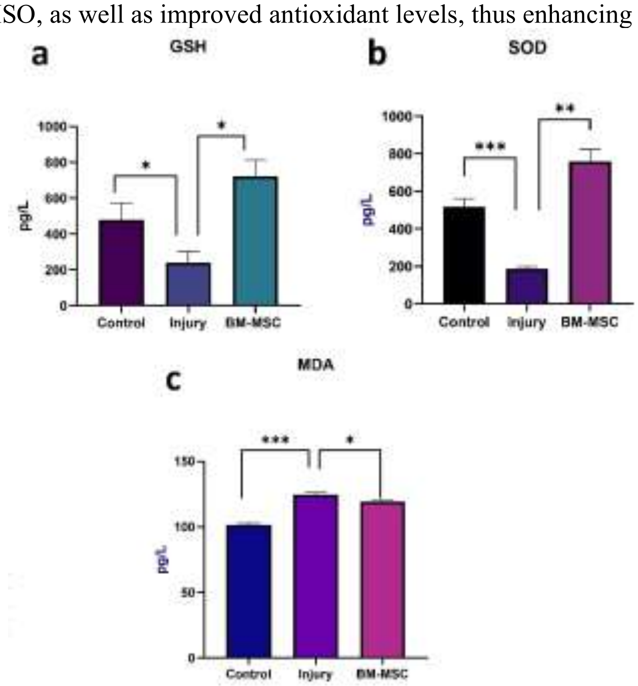

Figure 4. Effect of BM-MSC treatment on antioxidant and oxidative stress markers. (a) GSH levels (b), SOD levels (c), and MDA levels in all groups in vivo.

Results expressed in mean ± SD, * p=.010, ** p=.002, *** p <.001

3.4. Effect of BM-MSC treatment on gene expression analysis

Figure 4 depicts the effect of BM-MSC on the expression of cardiac-specific genes. As demonstrated in the figure, expression of cTnI, cTnT, and ANP was significantly increased in the MI group as compared to the BM-MSC group. These results were indicative of improvement in cardiac repair after BM-MSC treatment.

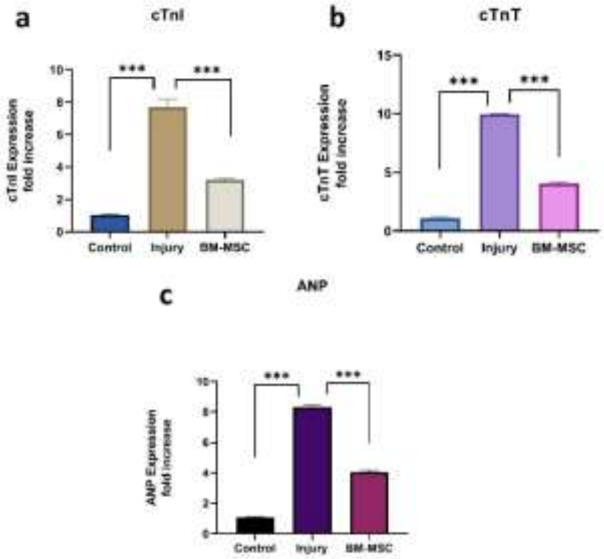

Figure 5. Effect of BM-MSC treatment on expression of cardiac-specific genes. (a) cTnI (b) cTnT (c) ANP fold increase in expression in all groups in vivo.

Results expressed in mean ± SD, *** p <.001

3.5. Histopathological analysis

Figure 6 (a-c) demonstrated the histopathological findings of all study groups. As demonstrated in Figure 6a, microscopic images of the control group with normal cardiac muscle architecture, normal nucleus shape and size, and normal membrane around muscle fibers. Figure 6b showed that ISO induced MI, with disruption of the muscle architecture, membrane destruction, leakage of red blood cells, marked myolysis, and multiple areas of necrosis were also present. Figure 6c showed the BM-MSC treated group, with normal cardiac muscle architecture and less myolysis, and more pronounced angiogenesis was present.

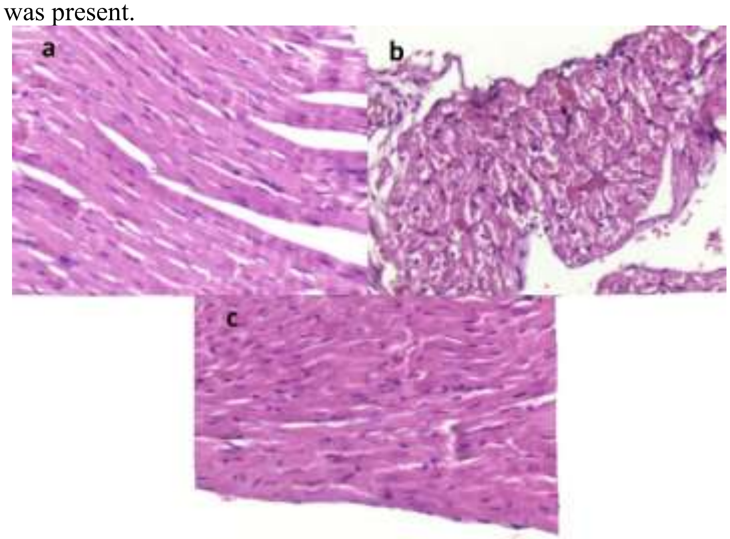

Figure 6. Histopathological analysis of the heart.

(a) Control group with normal cardiac muscle architecture, normal nucleus shape and size, and normal membrane around muscle fibers. (b) ISO-induced MI group with disruption of the muscle architecture, membrane destruction, leakage of red blood cells, marked myolysis, and multiple areas of necrosis (c) BM-MSC treatment group with normal cardiac muscle architecture and less myolysis, and more pronounced new vessels formation.

4. DISCUSSION

Myocardial infarction is an irreversible ischemic heart injury leading to permanent death of myocardial tissue, which ultimately leads to defective functions of the heart. Due to the limited regenerative potential of heart tissue, stem cell therapies have appeared as an aspiring agent for heart repair and regeneration (Weinberger & Eschenhagen, 2025). BM-MSCs have gained popularity in the treatment of MI as compared to other stem cell types. A previous study by Alzghoul et al. (2024) concluded that BM-MSCs have more prospects for cardiac repair and regeneration as compared to adipose-derived-MSCs. BM-MSC possesses the ability of cardiomyocyte differentiation owing to its paracrine, immunomodulatory, and antiinflammatory properties. The cardiac reparative properties of BM-MSC are mainly due to the modulation of the immune response by promoting the activity of M2 macrophages and suppressing the M1 macrophages. Thus promoting the release of anti-inflammatory mediators. Levels of antioxidants are also enhanced by BM-MSC transplantation in MI (Nazir et al., 2025). Due to the advantages of BM-MSCs, the present study utilized BM-MSCs as a novel therapeutic approach for MI repair.

In the present study, ISO was used to induce MI in a rat model. ISO was a reliable, non-invasive, and easy method for inducing MI in experimental animals. As reported by Gupta et al. (2024) that ISO-induced MI mimicked human MI, with similar histological and biochemical findings.

The mechanism underlying ISO-induced MI involved increased oxidative stress and depletion of antioxidant levels. In the present study, MDA levels were significantly higher in the MI group as compared to the control and BM-MSC-treated group. These findings were consistent with a study by Anwar Zarkasi et al. (2020), who reported that MDA levels were higher in the MI group than in the treatment group. Koçak et al. (2025) concluded that MDA levels were higher in MI animals after ISO administration and decreased after carvacrol treatment. In the current study, antioxidants (GSH, SOD) were significantly higher in the BM-MSC treatment group than in the MI group. These findings were consistent with previously reported studies showing that GSH and SOD levels improved after treatment with folic acid and Nattokinase (Pham et al., 2023; Sobot et al., 2024).

The ISO-induced oxidative stress leads to inflammation, which directly damages cardiac tissue and thereby worsens disease outcome. In the present study, TLC and CRP levels were markedly higher in the MI group. Levels were nearly normal in the BM-MSC-treated group. These findings were in accordance with previously reported studies, suggesting that TLC and CRP can be used as prognostic markers in MI (Mitsis et al., 2025; Smith et al., 2024). BM-MSC possesses anti-inflammatory properties, thus by reducing the inflammatory process in MI and promoting cardiac repair, as reported by Seow & Ling (2024)

The levels of cardiac biomarkers like cTnI, cTnT, CK-MB, LDH, and ANP reflect the cardiomyocyte membrane stability and permeability. The raised levels of the biomarkers were suggestive of increased permeability and hence membrane damage, and also associated with the severity of MI. As reported by Potter et al. (2022), who concluded that estimation of cTnI and cTnT served as important diagnostic and prognostic markers for MI. In this study, levels of these cardiac-specific biomarkers were significantly raised in the MI group as compared to the control and treatment groups. The levels were equal to normal in the BM-MSC-treated group. These findings were the same as those reported by Sajid et al. (2022), which demonstrated that levels of these cardiac-specific biomarkers were increased in the MI group and returned to normal when treated with Fumaria indica. BM-MSCs modulate the levels of cardiac-specific biomarkers, thus improving membrane integrity and permeability, and lead to cardiac regeneration and repair. The current study found that elevated expression of cTnI, cTnT, and ANP was present in the MI group. No study in the literature reported these findings. Our study showed elevated levels of ANP, CK-MB, and LDH. These findings were consistent with previously reported studies, which concluded that LDH, ANP, and CK-MB levels serve as prognostic markers for disease outcome (Jha et al., 2021; Rio Kurniawan et al., 2021; Zhu et al., 2024).

The cardiac reparative potential of BM-MSC was further supported by histopathological analysis of heart tissue in the current study. Normal cardiac architecture and cardiomyocytes with intact membranes were observed in the BM-MSC-treated group. The MI group showed multiple areas of necrosis and disruption of membrane integrity. These findings were in line with previously reported studies, which showed improved cardiac tissue histology after treatment (Flori et al., 2024; Sammeturi et al., 2020).

5. CONCLUSIONS

BM-MSC demonstrated enhanced cardiac reparative potential by modulating oxidative stress and cardiac biomarkers. This study concluded that BM-MSCs have cardio-protective and reparative effects in ISO-induced MI. Moreover, additional clinical and preclinical research is needed to investigate the molecular pathways that underlie the repair process.

6. Ethical Approval

The study was approved by the university's Review and Ethics Board (Ref-IMBB/BBBC/24/906-A). Before, during, and after the experiment, internationally accepted ethical guidelines for animal care, handling, and minimizing animal suffering were strictly followed. Moreover, the ARRIVE guidelines for in vivo experiments reporting were also followed (Klabukov et al., 2023). Both in vitro and in vivo experiments were included in our study.

7. Author’s contributions

Sadia Nazir: Formal analysis, Methodology, Writing – original draft, Data curation, Investigation; Tahir Maqbool: Supervision, Validation, Conceptualization; Mahwish Arooj: Review & editing; Sumeyra Savas: Review & editing; Muneer Imran: Review & editing.

8. Disclosure statement

No potential conflict of interest was reported by the author(s).

9. Funding

The research project did not receive any funding.

10. Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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